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Commentary

Quantifying Bronchodilator Responses in Chronic Obstructive Pulmonary Disease Trials

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Traditionally, the assessment of airflow limitation and acute reversibility in response to inhaled bronchodilator relies on spirometry, particularly the forced expiratory volume in 1 s (FEV_1). This variable is usually the primary outcome measure for clinical trials in patients with chronic obstructive pulmonary disease (COPD) since it is a simple, reproducible and inexpensive measurement [1]. There are limitations, however, to the use of FEV_1 as an endpoint in studies to asses the effect of bronchodilator drugs in COPD patients. For instances, measurement of FEV_1 requires a deep inhalation manoeuvre which may alter airway calibre [2]. Furthermore, FEV_1 correlates weakly with exercise capacity and dyspnoea, and changes in FEV_1 following bronchodilator therapy are poorly predictive of improved symptoms and exercise endurance [3]. Thus, exclusive reliance on the change in FEV_1 as the primary outcome measure in assessing therapeutic efficacy can lead to underestimation of a true clinical benefit in patient with COPD.

Body plethysmography is a well-established technique that allows also for the measurement of airway resistance and conductance, and is widely used in the assessment of bronchodilator efficacy in patients with COPD [4]. The impulse oscillation system (IOS) has been introduced as a user-friendly commercial version of the forced oscillation technique that provides a frequency-integrated measurement of total respiratory resistance and reactance [5]. Both these techniques do not require forced expiratory manoeuvres and are more sensitive than FEV_1 for measuring the bronchodilator response in both healthy subjects [6] and patients with asthma [7].

In this issue of the *Journal*, Borril *et al.* [8] have investigated the variability and sensitivity to bronchodilation of spirometry, IOS and body plethysmography in patients with COPD. They found that, although spirometry is more reproducible than IOS and body plethysmography, total respiratory resistance and reactance measured at the lower frequency range (5 Hz) by means of IOS, as well as plethysmographic airway resistance and conductance, are more sensitive than lung volumes and forced expiratory flows in detecting minimal bronchodilation following salbutamol administration. The results of the study are interesting and rise the question of the importance of the use of IOS and body plethysmography, rather than spirometry, in the evaluation of the bronchodilator response in COPD patients.

Some issues need to be taken into consideration when comparing the bronchodilator response measured by different lung function tests. It has been shown that the sensitivity to bronchodilation of different lung function tests depends on the method used to quantify the response [9]. When changes in lung function are expressed as percent of baseline, as is the case of the study by Borril et [8], respiratory resistance appears to be the most sensitive test, while, in contrast, spirometry is more sensitive when absolute changes are considered [9]. Furthermore, the cut-off level for a positive bronchodilator response, which is usually selected on the basis of the intraindividual coefficients of variation for a given lung function test, affects the sensitivity to bronchodilation of lung function tests [9]. Bronchodilation causes smaller changes in the values of spirometry than of respiratory resistances, but also the variability and, consequently, the cut-off level for a positive response is smaller for the former. Thus, it is unlikely that a single lung function test can be use to quantify the bronchodilator response. Although IOS and body plethysmography are practical methods for quantifying respiratory mechanics especially in noncooperative patients, measurements obtained with these lung function techniques cannot be interchangeable with those of spirometry. Further studies are needed to establish the actual clinical utility of IOS, particularly its relationship with exercise capacity and symptoms, in patients with COPD. It is my

opinion that, for a comprehensive therapeutic evaluation of bronchodilator therapy in patients with COPD, IOS is unlikely to obviate the need for measurements of lung hyperinflation, symptoms intensity and exercise endurance. The future development of a composite index that collectively incorporates these outcome measures may increase our ability to critically evaluate the clinical benefit of bronchodilator therapy in patients with COPD.

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